

Association between dietary salt and plasma glucose, insulin and hemoglobin A_{1c} levels among type 2 diabetes patients in Eastern China

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Abstract

Purpose

Type 2 diabetes (T2D) is one of the major public health concerns in China. Studies on the association between dietary salt intake and the glycaemia response of T2D are lacking in China. The aim was to investigate the association between the levels of dietary salt intake and the plasma glucose, insulin and hemoglobin A1c (HbA1c) in T2D patients.

Methods

Patients with T2D, who accepted management and treatment by the National Standardized Metabolic Disease Management Center at Ningbo First Hospital from March 2018 to January 2020, were included in this study. Dietary salt was collected through a standardized food frequent questionnaire. Anthropometry, blood pressure and biomarkers were measured by well-trained endocrinology nurses. Generalized linear models (GLM) were used to examine the association.

Results

A total of 1145 eligible T2D patients with the mean age of 51.4 years were included in the study. Fasting plasma glucose (FPG), 2h postprandial plasma glucose and 2h postprandial insulin, were significantly increased across dietary salt categories. Generalized linear models further showed that dietary salt > 8g/d were positively associated with FPG and HbA1c.

Conclusion

Higher daily salt intake was found to be associated with FPG and HbA1c in T2D patients. Lifestyle education and promotion on salt reduction should be provided to T2D patients.

Introduction

Over the past four decades, the rapidly increasing prevalence of type 2 diabetes (T2D) has become one of public health concerns in China due to the economic development, changes of diet, lifestyle and culture influenced by the westernization. The prevalence of diabetes was from less than 1% in 1980 ¹ to 12.8% in 2017. ² Currently, T2D has been the main driver for the increased prevalence of diabetes in China. ³ T2D patients in the tertiary hospital in Ningbo were reported to have poor glycemic control. ⁴ In addition, Li and his colleagues included 3370 T2D patients from the tertiary hospital in Ningbo indicated that patients with T2D were at high risk of further chronic complications including hypertension, dyslipidemia nephropathy, retinopathy, coronary heart disease stroke and cerebrovascular diseases. ⁵

T2D is a lifestyle disorder and progression is highly correlated with aging, dietary and lifestyle behavior, and genetic factors.⁶ Although dietary salt as an essential seasoning contributes to eating pleasure and satisfaction⁷, many guidelines have promoted dietary salt restriction in patients with diabetes.⁸⁹ Higher intake of sodium is an established risk factor for stroke and cardiovascular diseases.¹⁰ Dietary sodium intake is evidenced to be positively associated with increased blood pressure in the general population.¹¹¹² However, the connection between dietary salt and glucose homeostasis remains elusive and has not been drawn the same attention as hypertension. The majority of dietary interventions did not focus on the relationship of dietary salt/sodium intake with the prognosis of diabetes.

To our best knowledge, few studies have explored the relationship between dietary salt and T2D in China. The objective of this study was to investigate the association between the levels of dietary salt and blood glucose, insulin and hemoglobin A_{1c} (HbA_{1c}) of T2D patients in Ningbo, China.

Methods

Study design and participants

An ongoing innovation study of the management of metabolic diseases and complications is a national standardized project, implemented by the Metabolic Management Center (MMC). National standardized MMC, called “One Center, One Stop, and One Standard Model” was established as a platform with standardized diagnosis and treatment of metabolic diseases and their long-term follow-up.¹³ In the MMCs, patients can receive a comprehensive series of services including registration, tests, evaluation, prescriptions and health education. Under the guidance of the MMC, Experts Committee, more than 400 stringent standard operating procedures were set up for quality control of the MMC operation. The details of national MMC were reported elsewhere.¹³

The present study included 2313 patients with T2D, registering MMC at the first time, from March 2018 to January 2020 at the outpatient Department of Endocrinology, Ningbo First Hospital, Zhejiang Province, China and the National Standardized MMC. T2D was diagnosed based on the definition proposed by the World Health Organization (WHO).¹⁴ Patients were excluded from this study if: (1) age > 75 years and age < 18 years; (2) diagnosis with any kind of cancer; (3) positive islet autoantibodies; (4) glomerular filtration rate (eGFR) < 30 mL/min; (5) severe liver dysfunction; (6) acute infectious diseases; (7) pregnancy or lactation; (8) incompleteness of standardized questionnaires of food frequent questionnaire (FFQ), demography and lifestyle.

The study was approved by the Research Ethics Committee of Ningbo First Hospital, China (No. 2019-R057). Written informed consents were obtained from all the participants.

Dietary assessment

Dietary information was collected through a national-wide standardized FFQ, following the guidelines proposed by MMC and Ningbo First Hospital during outpatient visits. All the dietary information was

collected by well-trained nurses. Quantitative dietary information was collected on how many usual foods (vegetables, fruits, soya and soya products) was consumed per gram per day, how often meats (red meat, poultry, fish and shrimp) and soft drinks were consumed per week, and how much seasoning (salt and sugar) was consumed per day. Patients were provided a standard brochure with colorful photographs for description of the portion sizes following the guideline Chinese dietary guideline.¹⁵ Considering the psychological responses of patients, all the information on dietary intakes were collected through multiple choices.

Dietary salt was categories into 3 groups: $\leq 6\text{g/d}$, $6\text{-}8\text{g/d}$ and $> 8\text{g/d}$. The missing reports were asked to fill in during outpatient visits and the misreports were evaluated and corrected based on daily reasonable consumption.

Demography and lifestyle

All adults diagnosed with T2D, willing to participate in the study, were invited to complete the MMC standard questionnaires on their demography [education (low education: lower than colleagues/universities and high education: colleagues/universities or above)], lifestyle [current smoking status (no and yes); current drinking alcohol status (no and yes); physical activity], medical history and medication records.

Anthropometric measurements and blood pressure

Anthropometric measurements included height, body weight and waist circumference (WC) were measured with light clothing by well-trained endocrinology nurses. Height to the nearest 0.1cm and body weight to the nearest 0.1kg were measured using an electronic scale (ORMON HNF-318). WC was measured at the midpoint between the inferior costal margin and the iliac crest in the midaxillary line. BMI, defining a general obesity, was calculated as weight (kg) / height (m^2). Patients were classified into four BMI categories according to China Obesity Task Force as follows: underweight ($< 18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}23.9 \text{ kg/m}^2$), overweight ($24.0\text{-}27.9 \text{ kg/m}^2$), and obesity ($\geq 28.0 \text{ kg/m}^2$).¹⁶ Abdominal obesity was defined according to WC values: WC $> 90 \text{ cm}$ in men or $> 85\text{cm}$ in women.¹⁶ Blood pressure was measured using an electronic sphygmomanometer on the right or left arm after a 10-minute rest.

Biomarker measurements

After a 10-12h-overnight fasting, blood samples were obtained in the early morning to measure the levels of blood profiles including fasting plasma glucose (FPG), fasting insulin (FINS), glycated hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA) and serum creatinine (Scr). Then the 100g carbohydrate (steamed bread meal) test was used to assess 2 hour postprandial plasma glucose (2hPG) and 2 hour postprandial insulin (2hINS) concentrations.

FPG and 2hPG were assessed by the glucose oxidase method and chemiluminescence immunoassay, respectively. FINS was measured by radioimmunoassay. HbA1c was determined by high-pressure liquid chromatography. UA was examined by enzymatic spectrophotometry. Details of biomarker measurements were reported somewhere.¹⁷

Statistical analysis

The percentage of patients, mean with standard deviation (SD) and median values with interquartile range among the categories of dietary salt were presented as descriptive analysis. ANOVA with Bonferroni correction/ Games-Howell, and Mann-Whitney U test and Kruskal-Wallis were used to examine mean and median values of anthropology and biomarkers within and between the categories of dietary salt.

Generalized linear models (GLM) were used to assess associations of salt intakes with biomarkers (FPG, 2hPG, FINS, 2hINS and HbA1c) after adjusting for confounding factors (sex, age and education levels), lifestyle factors (physical activity, smoking status and drinking status), BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), UA, Scr, medication and interactions. Significant interactions between dietary salt and confounding factors were only examined in the model. Results were considered statistically significant at a two-tailed level of 0.05. Statistical analyses were conducted using IBM SPSS Statistics version 26.0.

Results

Study population

In total, 1145 out of 2313 T2D patients (65.2% men) with a mean age of 51.4 years old were included in the present study and divided into three groups according to salt intake: $\leq 6\text{g/d}$, 6-8g/d and $> 8\text{g/d}$ (Table 1).

Among all patients, around 25.0% patients had dietary salt intake less than or equal to 6g/d. Compared to lower salt intake ($\leq 6\text{g/d}$), the higher prevalence of overweight and central obese patients was observed in the group of higher salt intakes (6-8g/d and $> 8\text{g/d}$). Similarly, the higher prevalence of hypertension, hyperlipidemia, hyperuricemia and coronary disease was in the group of higher salt intakes.

Risk factors among salt intake categories

In T2D patients, direct risk factors including FPG, 2hPG, 2hINS and HbA1c and indirect risk factors including BMI, WC, VFA, SFA, TC, TG and LDL-C were significantly different across dietary salt categories (Table 2), whereas, 2hINS, SBP, DBP, HDL-C and UA, were not found significant difference. Within dietary salt categories, mean values of FPG, 2hPG and HbA1c were significantly higher in the group of dietary salt $> 8\text{g/d}$ than the values in the group of lower salt intake categories ($\leq 6\text{g/d}$ and 6-8g/d).

Associations between dietary salt intake and blood glucose, insulin and HbA1c

Associations of dietary salt with plasma glucose, insulin and HbA1c among T2D patients were further investigated by GLM (Table 3, Table 4 and Table 5). Dietary salt (6-8g/d and >8g/d) was significantly associated with all the dependent variables (FPG, 2hPG, FINS, 2hINS and HbA1c) in the crude model. After further adjusting for confounding factors, lifestyle factors, BMI, WC, SBP, DBP, UA, Scr, medication and interactions, dietary salt (>8g/d) was remained statistically significance in the model and positively associated with FPG ($\beta = 2.3$, $P = 0.013$) and HbA1c ($\beta = 0.67$, $P = 0.032$). Therefore, the results showed that higher dietary salt >8g/d increased 2.3 mmol/L FPG and 0.67% HbA1c, compared to lower dietary salt ≤ 6 g/d.

Discussion

To date, the association of dietary salt intake with the glycaemia response of T2D was not well investigated and understood in China, in T2D patients in particular. The present study, using clinical data of the outpatient department of the Endocrinology and MMC, was to analyze the association of dietary salt and the glycaemia response of T2D (plasma glucose, insulin and HbA1c) in T2D patients in Ningbo. The findings indicated that higher dietary salt was positively associated with increasing FPG and HbA1c.

One previous study conducted on Ningbo healthy residents in Ningbo showed that higher fasting blood glucose level was found in the group of higher dietary salt intake (≥ 6 g/d) compared to it in the group of dietary salt (<6g/d).¹² The results of the Chinese study are in line with our findings on FPG among Chinese in Ningbo, although target populations are different. The mechanism of the association between dietary salt and the glycaemia response in T2D patients is unclear yet. Increasing dietary salt intake may suppress activities of the renin-angiotensin-aldosterone system^{18 19} and stimulate sympathetic activity²⁰ and cause insulin resistance.^{21 22} Therefore, it may contribute to the development and progression of T2D complications.

The majority studies on the relationship between dietary salt and the glycaemia response of T2D have been explored through observational studies, intervention studies and meta-analysis among healthy population.^{12 23 24} However, few studies have been conducted on T2D patients. Our findings showed that dietary salt was positively associated with HbA1c, which is consistent with the results from one randomized controlled trial (RCT) on salt reduction.²⁴ This observer-blind RCT recruiting 70 patients with acute non-cardio-embolic mild ischemic stroke reported that HbA1c decreased more in the lifestyle intervention group providing reduction in salt intake compared to controlled group, although no significant difference was found between 2 groups.²⁴ Likewise, Strazzullo and his colleagues conducting a meta-analysis including 13 studies with 177025 participants indicated an effect between the HbA1c level and dietary sodium for the development of CVD.²⁵

Higher dietary salt was found to be related to high prevalence of overweight and obesity compared to lower dietary salt in the present study. Additionally, high blood lipid levels were significantly related to increasing dietary salt intake in our study. The potential hypothesis is that high dietary salt might increase plasma glucose and postprandial plasma glucose in T2D patients through weight gain due to appetite and over-consumption of energy, fat and cholesterol.²⁶ Eventually, increased fat free acid level in blood can inhibit insulin suppression of hepatic glucose production.²⁷ Dietary salt is a key factor to increase the feeling of thirsty, resulting in more amount of fluid drinks.²⁸ Increasing 1 g/d dietary salt intake was positively associated with an increase in 100 g/d total fluid and 27 g/d sugar-sweetened soft drink consumption.²⁹ Hereby, it may contribute to high blood pressure/hypertension.

Several dietary guidelines recommend and advocate that patients with T2D should decrease their dietary salt intake due to benefits for lowering a modest blood pressure.⁸⁹ In the present study, the results derived from description analysis showed that no significant difference in SBP and DBP was found across dietary salt categories. The WHO Cardiovascular Diseases and Alimentary Comparison (WHO-CARDIAC) Study conducted on pre- and post-menopausal women from 17 countries and reported that 24 h sodium excretion was positively associated with blood pressure.³⁰ In T2D patients, hypertension is associated with a range of adverse outcomes for further developing cardiovascular disease and premature mortality.³¹ The different result in our study might be attributed to the nature of cross-sectional study design.

Interestingly, dietary salt was not found to be significantly associated with postprandial plasma glucose and postprandial insulin. Few studies have been investigated on the relationship between dietary salt, and postprandial plasma glucose and insulin responses in T2D patients. An intervention study including six healthy adults, assigned randomly meals with or without added salt, suggested that moderate dietary salt intake increased postprandial plasma glucose and insulin levels.²³ Sodium can facilitate the absorption of glucose in the small intestine.³² The potential reason can be that most of our participants had been diagnosed with T2D for a certain period so that postprandial plasma glucose and insulin responses to dietary salt cannot be the same like healthy participants due to insensitive digestion system.

The relationship between dietary salt intake and hypertension has been well understood in Chinese population. In addition, the knowledge on glycaemia control through the duration and the quantity of carbohydrate consumption from foods is understood as well.³³ Patients with diabetes are recommended to restrict total consumption of energy and carbohydrates in order to control body weight and blood glucose levels. However, the knowledge of the effect of dietary salt intake on the glycaemia response in T2D patients needs to get more attention. Therefore, hospital-based education and community-based education are necessarily required regarding health effects of excess salt intake, food labelling and food sources.

This is the first study on the association between dietary salt intake and the glycaemia response in T2D patients in Ningbo with standard national management and treatment by MMC. Nevertheless, several study limitations need to be considered. First, causality between dietary salt intake and factors of T2D

cannot be achieved according to the nature of cross-sectional study design. Second, because of the structure of FFQ, quantitative dietary salt intake could not be obtained, although the categories of salt intake could be collected from the patients. Therefore, it may not accurately reflect daily dietary salt intake among T2D patients. Third, total energy intake was not adjusted in the model due to FFQ. Additionally, the reported dietary salt level could be biased towards misreporting because of patients' psychology. Furthermore, due to patients from Eastern China, so the findings cannot be representative for the entire Chinese population with T2D.

Conclusion

High dietary salt intake was found to be associated with FPG and HbA1c among T2D patients. Hospital-based lifestyle education promotion on salt reduction should be provided to T2D patients. Intervention study on salt reduction should be carried out to investigate the impact of the dose of dietary salt intake on the glycaemia response of T2D patients for future research.

Declarations

Acknowledgments

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Ethics Statement

The study was ethically approved by the Ethics Committee of Ningbo First Hospital, China (Ethics Approval No. 2019-R057) and followed the Declaration of Helsinki.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declared no conflicts of interest for this work.

Author Contributions

LL contributed to the study design for the whole research. LY performed and interpreted statistical analysis and drafted manuscript writing. KC and LJL was supporting the manuscript writing. YX, CYS, and ZY were responsible for data collection and quality control.

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Tables

Table 1. Participant characteristics according to levels of salt intake

	Total (n=1145)	≤6g/d (n=286)	6-8g/d (n=443)	≥8g/d (n=416)
	<u>Mean (SD).</u>			
Age (years)	51.4 (11.7)	50.9 (12.3)	51.8 (11.4)	51.3 (11.6)
Duration of type 2 diabetes (years)	7.5 (6.4)	7.4 (6.7)	7.8 (6.3)	7.2 (6.4)
Physical activity (minutes/week)	464.2 (1217.6)	481.3 (928.3)	481.7 (1542.3)	433.5 (979.6)
	<u>No. (%).</u>			
Male	746 (65.2)	178 (62.2)	284 (64.1)	284 (68.3)
Education				
High education	608 (53.1)	152 (53.1)	243 (54.9)	213 (51.2)
Currently smoking status				
No	782 (68.3)	214 (74.8)	301 (67.9)	267 (64.2)
Yes	363 (31.7)	72 (25.2)	142 (32.1)	149 (35.8)
Currently drinking status				
No	654 (57.1)	189 (66.1)	247 (55.8)	218 (52.4)
Yes	491 (42.9)	97 (33.9)	196 (44.2)	198 (47.6)
Weight status				
Underweight	243 (21.2)	63 (22.0)	76 (17.2)	104 (25.0)
Normal weight	414 (36.2)	109 (38.1)	177 (40.0)	128 (30.8)
Overweight	480 (41.9)	113 (39.5)	185 (41.8)	182 (43.8)
Obesity	8 (0.7)	1 (0.3)	5 (1.1)	2 (0.5)
Waist circumference status				
Central obesity	482 (42.1)	138 (48.3)	214 (48.3)	260 (62.5)
Hypertension	453 (39.6)	105 (36.7)	170 (38.4)	178 (42.8)
Hyperlipidemia	600 (52.4)	148 (51.7)	231 (52.1)	221 (53.1)
Hypeluricemia	202 (17.6)	45 (15.7)	75 (16.9)	82 (19.7)
Coronary disease	48 (4.2)	12 (4.2)	22 (5.0)	14 (3.4)

Stroke	37 (3.2)	13 (4.5)	13 (2.9)	11 (2.6)
Medication for hypertension*	417 (36.7)	97 (33.9)	157 (35.4)	163 (39.2)
Medication for hyperlipidemia*	316 (27.6)	89 (31.1)	118 (26.6)	109 (26.2)
Medication for hyperuricemia*	30 (2.6)	8 (2.8)	12 (2.7)	10 (2.4)

SD: standard deviation

* The total sample of medication for hypertension was 1140; the total sample of medication for hyperlipidemia and the medication for hyperuricemia was 1142.

Table 2. Mean and median values of risk factors of type 2 diabetes according to salt intake levels

Factors*	≤6g/d (n=286)	6-8g/d (n=443)	≥8g/d (n=416)	P
BMI (kg/m ²)	25.2 (3.8)	24.9 (3.6)	25.9 (3.8) ^{ad}	<0.001
WC (cm)	87.6 (10.6)	87.9 (9.7)	90.4 (9.5) ^{bd}	<0.001
VFA (cm ²)	87.7 (40.1)	89.9 (40.3)	99.8 (38.7) ^{bd}	<0.001
SFA (cm ²)	175.9 (3.9)	174.0 (60.6)	189.0 (64.6) ^{ac}	0.001
SBP (mmHg)	133.1 (17.7)	131.2 (17.7)	133.8 (18.3)	0.088
DBP (mmHg)	79.3 (11.5)	78.8 (11.0)	79.8 (10.6)	0.405
FPG (mmol/L)	8.1 (3.0)	8.7 (2.9)	8.9 (3.0) ^{ac}	0.005
2hPG (mmol/L)	12.6 (4.7)	14.0 (5.6) ^b	14.2 (5.0) ^d	<0.001
FINS (mIU/L)	11.2 (13.8)	12.6 (42.0) ^a	12.2 (38.8)	0.048
2hINS (mIU/L)	38.2 (54.3)	43.0 (137.0)	44.9 (114.6)	0.194
HbA1c (%)	7.6 (1.9)	8.2 (2.1) ^b	8.4 (2.0) ^d	<0.001
TC (mmol/L)	4.4 (1.1)	4.6 (1.2)	4.7 (1.3) ^b	0.002
TG (mmol/L)	1.3 (1.1)	1.4 (1.2) ^a	1.6 (1.2) ^b	0.006
LDL-C (mmol/L)	2.8 (0.851)	2.9 (0.865)	3.0 (0.910) ^c	0.006
HDL-C (mmol/L)	1.2 (0.303)	1.2 (0.288)	1.1 (0.272) ^c	0.05
Uric acid (mmol/L)	327.4 (89.8)	329.9 (89.4)	330.9 (85.6)	0.87

BMI, body mass index; WC, waist circumference; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2hPG, 2 hour postprandial plasma glucose; FINS, fasting plasma insulin, 2hINS, 2 hour postprandial plasma insulin; HbA1c, glycated hemoglobin A1c.

*FINS, 2hINS and TG were presented as median values with interquartile range and the rest factors were presented as mean values with standard deviation.

^a Significant difference from salt intake ≤6g/d, P < 0.05

^b Significant difference from salt intake ≤6g/d, P ≤ 0.001

^c Significant difference from salt intake 6-8g/d, P < 0.05

^d Significant difference from salt intake 6-8g/d, $P \leq 0.001$

Table 3. Association of dietary salt intakes and plasma glucose

Salt intake*	β	95% CI	P
<u>Fasting plasma glucose</u>			
Crude mode			
6-8g/d	0.538	0.095, -0.292	0.017
>8g/d	0.731	0.292, 1.2	0.001
Adjusted model ^a			
6-8g/d	1.4	-0.442, 3.1	0.139
>8g/d	2.3	0.472, 4.1	0.013
<u>2 hour postprandial plasma glucose</u>			
Crude mode			
6-8g/d	1.4	0.625, 2.2	<0.001
>8g/d	1.5	0.742, 2.3	<0.001
Adjusted model ^a			
6-8g/d	2.3	-0.960, 5.6	0.166
>8g/d	1.5	-1.8, 4.8	0.38
β , beta-coefficient; CI, confidence intervals			
* ≤ 6 g/d salt intake is reference category in the model			

^a Adjusted for sex, age, education, physical activity, smoking, drinking, creatinine, uric acid lipid lipids, medication and interactions

Table 4. Association of dietary salt intakes and insulin

Salt intake*	β	95% CI	P
<u>Fasting insulin</u>			
Crude mode			
6-8g/d	20.3	7.7, 32.9	0.002
>8g/d	7.5	-5.3, 20.2	0.251
Adjusted model ^a			
6-8g/d	-22.7	-78.3, 32.8	0.422
>8g/d	-0.274	-56.1, 55.5	0.992
<u>2 hour postprandial insulin</u>			
Crude mode			
6-8g/d	47.7	19.7, 75.6	0.001
>8g/d	22.8	-5.6, 51.1	0.116
Adjusted model ^a			
6-8g/d	-73.7	-163.2, 77.6	0.229
>8g/d	-42.8	-193.6, 46.3	0.486
β , beta-coefficient; CI, confidence intervals			
* \leq 6g/d salt intake is reference category in the model			

^a Adjusted for sex, age, education, physical activity, smoking, drinking, creatinine, uric acid lipid lipids, medication and interactions

Table 5. Association of dietary salt intake and HbA1c

Salt intake ^{a*}	β	95% CI	P
Crude mode			
4-6g/d	-0.15	-0.81, 0.51	0.653
6-8g/d	0.43	-0.21, 1.1	0.188
>8g/d	0.64	0.002, 1.3	0.049
Adjusted model ^a			
4-6g/d	-0.1	-0.75, 0.55	0.754
6-8g/d	0.44	-0.18, 1.1	0.162
>8g/d	0.67	0.04, 1.3	0.032

β , beta-coefficient; CI, confidence interval; HbA1c, glycated hemoglobin A1c

* \leq 6g/d salt intake is reference category in the model

^aAdjusted for sex, age, education, physical activity, smoking, drinking, creatinine, uric acid lipid lipids, medication and interactions